BJP British Journal of Pharmacology

DOI:10.1111/bph.12362
www.brjpharmacol.org

Themed Section: Biological Sex and Cardiovascular Pharmacology

REVIEW

Pharmacogenomics, pharmacokinetics and pharmacodynamics: interaction with biological differences between men and women

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Keywords
sex differences; gender differences; drug response; pharmacodynamics; pharmacokinetic

Received
13 February 2013
Revised
5 August 2013
Accepted
16 August 2013

Pharmacological response depends on multiple factors and one of them is sex–gender. Data on the specific effects of sex–gender on pharmacokinetics, as well as the safety and efficacy of numerous medications, are beginning to emerge. Nevertheless, the recruitment of women for clinical research is inadequate, especially during the first phases. In general, pharmacokinetic differences between males and females are more numerous and consistent than disparities in pharmacodynamics. However, sex–gender pharmacodynamic differences are now increasingly being identified at the molecular level. It is now even becoming apparent that sex–gender influences pharmacogenomics and pharmacogenetics. Sex-related differences have been reported for several parameters, and it is consistently shown that women have a worse safety profile, with drug adverse reactions being more frequent and severe in women than in men. Overall, the pharmacological status of women is less well studied than that of men and deserves much more attention. The design of clinical and preclinical studies should have a sex–gender-based approach with the aim of tailoring therapies to an individual's needs and concerns.

LINKED ARTICLES
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Abbreviations
ACEI, inhibitor of angiotensin converting enzyme; ADE, adverse drug effect; ARB, antagonist of angiotensin receptor 1; CV, cardiovascular; CYP, cytochrome P450 enzymes; ET-1, endothelin-1; HMG-CoA, hydroxymethylglutaryl coenzyme A; OC, oral contraceptives; RAS, renin angiotensin system; SGD, sex–gender difference

Introduction

Optimal pharmacological therapy depends on many factors. Some of these factors are biological (metabolism, genetic and epigenetic backgrounds, age and sex) (Becquemont *et al.*, 2006), while others depend on the environment such as care provider-patient relationship. In view of the numerous biological (sex) and psychosocial-cultural (gender) differences, women and men can be considered as two different categories (Legato, 2009). However, sex–gender difference (SGD) only started to acquire the right relevance in the latter part of the last century, although Hippocrates, describing the symptoms of gout, had written '*A woman does not take the gout unless her menses has stopped*' (Enomoto and Endou, 2005), indicating a SGD in susceptibility rather than the development of a disease. The first pharmacological SGD was described in 1932 (Nicholas and Barron, 1932), when it was demonstrated that the hypnotic effect of hexobarbital lasted longer in female than in male rats. Later, it was shown that this difference is dependent on the metabolic process (Quinn *et al.*, 1958). Nowadays, SGDs in pharmacokinetic parameters are well known and have been recently and extensively

reviewed (Gandhi *et al.*, 2004; Anderson, 2005; Franconi *et al.*, 2007; 2011a,b; Soldin and Mattison, 2009). The SGDs in pharmacodynamics are not so well-known, but they are now emerging and have been recently reviewed (Legato, 2009; Maselli *et al.*, 2009; Franconi *et al.*, 2011a,b; Regitz-Zagrosek, 2012; Wang *et al.*, 2012; Marazziti *et al.*, 2013). Numerous data suggest a link between genetic polymorphisms and drug effects (Bochud and Guessous, 2012; Myburgh *et al.*, 2012), but relatively little is known about the interaction of sex–gender and pharmacogenetics on drug activity and patient outcomes. For example, hormonal substitutive therapy is associated with a significant risk to women with the platelet glycoprotein GPIbα-TT and GP VI-TC/CC genotypes but is of benefit to women with GPIbα-TC/CC and GP VI-TT genotypes (Bray *et al.*, 2007).

Finally, some SGDs are caused by social, educational, cultural and lifestyle factors (e.g. smoking and alcohol habits), stress, access to health care and service (Glaser *et al.*, 2000; Budesa *et al.*, 2008). In line with previous observations, poverty, low social status, domestic violence and caregiver role are related to the stress response, which lead to CV disease and diabetes mellitus (Krantz *et al.*, 1981; Muller *et al.*, 1994; Ghiadoni *et al.*, 2000; Carney *et al.*, 2001; Veronesi *et al.*, 2010; Elovainio *et al.*, 2011). Overall, these considerations strongly suggest that sex and gender are strictly and constantly associated (Marino *et al.*, 2011; Springer *et al.*, 2011). Indeed, gender is related to genetic and epigenetic variations (El-Maarri *et al.*, 2007; Zhang *et al.*, 2011a; Campesi *et al.*, 2013) that have different effects on the male and female body (Kaminsky *et al.*, 2006). It has also been found that gender can affect responses to xenobiotics (Campesi *et al.*, 2013).

Effect of diseases, access to care, influence of physician's and patient's sex on treatment and adherence

It is still not clear whether pathological conditions, such as renal, hepatic, cardiac failure and diabetes mellitus, affect pharmacodynamic and pharmacokinetic parameters in a sex–gender dependent way (Shammas and Dickstein, 1988; Hanley *et al.*, 2010; Dostalek *et al.*, 2012). However, adverse drug effects (ADEs) in heart failure occur in a sex–gender-specific manner being more prevalent in women than in men (Catananti *et al.*, 2009). Therefore, studies are needed to better understand the influence of the sex–gender element on pharmacokinetic and pharmacodynamic variations induced by pathological conditions. The therapeutic response partially depends on access to healthcare systems and psychosocial factors. The former seems to be influenced by patient sex; it has been shown that access to primary therapy for acute coronary syndrome is less easy for women than for men (Lee *et al.*, 2008; El-Menyar *et al.*, 2009; Halvorsen *et al.*, 2009). Notably, the number of drug prescriptions appears to be influenced by the sex of patients (Enriquez *et al.*, 2008) and also by the sex of the care provider; diabetic women treated by female physicians are more likely to reach their treatment goals than if treated by men (Journath *et al.*, 2010). Interestingly, being a woman is a negative predictor for therapy adherence after acute coronary syndrome and myocardial infarction (Butler *et al.*, 2002; Jackevicius *et al.*, 2008; Lee *et al.*, 2008; Peterson *et al.*, 2008; Tuppin *et al.*, 2009; Mosca *et al.*, 2011; Kirchmayer *et al.*, 2012; Kumbhani *et al.*, 2013), and in hypertension (Mazzaglia *et al.*, 2009). This finding could partly be as a result of there being more women in the elderly population than men (Mazzaglia *et al.*, 2009). However, these findings do suggest that there is a need for physicians to adopt specifically tailored programmes to improve evidence-based care in women with acute myocardial infarction. A better awareness of all the components that influence treatment and adherence could improve clinical outcomes in women with CV disease.

Is the actual clinical trial design able to incorporate SGDs?

Nowadays, it is clear that sex–gender potentially affects a multitude of parameters from conception to death (Institute of Medicine, 2010), and so this dimension should be considered in the design, enrolment, analysis and reporting of data to avoid slowing down progress in improving health and medicine. It is evident that consideration of SGDs is critical in the development of medications, and therefore both men and women should be enrolled in clinical investigations. Nowadays, with the exception of CV diseases and sex-unrelated cancers, women are routinely recruited, at least in phase 3 clinical trials (Raz and Miller, 2012). However, there are still fewer females than males participating in phase 1 and phase 2 trials (Pinnow *et al.*, 2009), despite the regulatory agencies of USA and Canada stipulating that women should be included in clinical trials (Health Canada, 1997; FDA, 2010).

Phase 1 clinical trials of a drug start when sufficient animal data have been accumulated establishing that the compound has a reasonably safe profile and is likely to have a therapeutic effect. Therfore, it is necessary to have experimental animal models that are predictive for SGDs in humans, but suitable models are not always available (Mugford and Kedderis, 1998; Franconi *et al.*, 2008; Mahmoodzadeh *et al.*, 2012). The limited recruitment of women, under-utilization of female animals and the use of non-predictive models in preclinical studies all contribute to a lack of knowledge and awareness of SGDs in drug response. Also, difficulties in the translation of data obtained in males to females ultimately leads to less appropriate therapy for women (Johnell *et al.*, 2009). So, both preclinical and clinical studies require a sex–gender approach in the development of drugs in order to improve translational medicine (Raz and Miller, 2012). Hence, the cyclic hormonal fluctuations of females and the events of reproductive life (pregnancy and lactation), which now contribute to the exclusion of women from clinical trials and of female animals from preclinical studies (Miller *et al.*, 2011; Spoletini *et al.*, 2012), should be incorporated in the experimental paradigms. Indeed, pregnancy produces important changes in the female body that might modify pharmacokinetic parameters of medications (Anger and Piquette-Miller, 2008), and considering that 96% of pregnant women consume at least one drug (Weiner *et al.*, 2005), this is an imperative problem.

Endogenous and exogenous sexual hormones can affect pharmacodynamics and pharmacokinetics directly and indirectly, as sex hormones affect drug responses and some drugs modify hormonal signalling pathways (Franconi *et al.*, 2007; Spoletini *et al.*, 2012). Numerous reviews have focused on strategies and methods that optimize sex–gender research in different fields (Gillies and McArthur, 2010; Miller *et al.*, 2011). However, to optimize the design of clinical studies, identification of the role sex-gender has in the placebo response is urgently required (Saxon *et al.*, 2001; Franconi *et al.*, 2007; 2012; Greenspan *et al.*, 2007; Aslaksen and Flaten, 2008; Haltia *et al.*, 2008; Aslaksen *et al.*, 2011), either for the investigators or for the patients, because the placebo effect may be an integral part of the therapy (Ross and Buckalew, 1985). Although at this stage it has not been possible to reach any firm conclusions, in view of the importance of social factors and the biological differences involved in the placebo effect, SGDs are plausible.

Pharmacokinetic differences including bioequivalence studies

The SGDs in pharmacokinetics have been recently reviewed (Gandhi *et al.*, 2004; Anderson, 2005; Schwartz, 2007; Franconi *et al.*, 2011a,b; Wang *et al.*, 2012), and they include all pharmacokinetic parameters. A great number of SGDs have been demonstrated in the gastrointestinal system; for example gastric pH is higher in women than men, whereas gastric and bowel transit times are lower (Freire *et al.*, 2011). Some of these differences are progesterone- and oestrogen-dependent, being influenced by the phase of the menstrual cycle or pregnancy. Luminal pH and gastrointestinal motility can have a significant effect on drug bioavailability, influencing the rate of drug dissolution and the transit time, which could lead, for example, to an increased waiting time for taking the drug after meals. Some SDGs in metabolic enzymes are reported in Table 1, many of which concern isoforms of the cytochrome P450 system belonging to 1, 2 and 3 CYP families, which catalyze the oxidative biotransformation of many drugs. Indeed, sex-specific expression of CYP isoforms is common in rodents (Waxman and Holloway, 2009), but is more subtle in humans (Gandhi *et al.*, 2004; Schwartz, 2007; Waxman and Holloway, 2009; Zhang *et al.*, 2011b). The most important CYP isoform in drug metabolism is CYP3A4, which has a higher level of expression in female livers than in males (Parkinson *et al.*, 2004; Waxman and Holloway, 2009). Table 1 also shows SGDs in transporters and multiple drug resistance proteins. Genetic polymorphisms of drug transporters have been demonstrated extensively (Buist *et al.*, 2002; Morris *et al.*, 2003; Groves *et al.*, 2006; Burckhardt, 2012; Emami Riedmaier *et al.*, 2012). Expression of P-glycoprotein, also known as multidrug resistance protein, differs between men and women; for example hepatic expression is 2.4-fold lower in females, although there are large inter-individual differences in P-glycoprotein levels (Schuetz *et al.*, 1995). However, little is known about SGDs in P-glycoprotein function at the blood–brain barrier, which again may be influenced by sex-gender-specific hormones (Bebawy and Chetty, 2009). Although it has been shown that age induces a decline in the P-glycoprotein function of the blood–brain barrier in men but not in women (van Assema *et al.*, 2012).

Considering that a great number of drugs can be found in generic form, we recollect that bioequivalence studies of the generic versus reference drug are carried out mostly in adult young men (European Medicines Agency, 2010), disregarding the fact that these drugs are also used by women. However, the inactive ingredients may affect the bioavailability of generics and this could occur in a sex-specific way, at least in some cases. For example, polyethylene glycol enhances the bioavailability of ranitidine in men (up to 63%), whereas it is decreased in women (up to 24%) (Ashiru *et al.*, 2008). Furthermore, women may develop more ADEs than men arising from different inactive ingredients (Kando *et al.*, 1995; Soldin *et al.*, 2011), which may affect the safety profile of a medication. In conclusion, SGD should also be included as a variable in bioequivalence studies (Wolbrette, 2002), especially for drugs that prolong QT interval and have a narrow therapeutic index.

Pharmacodynamics and pharmacogenomics

The SGDs in pharmacodynamics are more difficult to demonstrate because more male than female animals are used in experimental studies, while cells are often considered to be without sex (Maselli *et al.*, 2009; Miller *et al.*, 2011). However, in the last few years, the number of studies demonstrating SGDs at the molecular level has increased, and numerous pharmacological targets have been investigated (Antoniucci *et al.*, 2001; Drici and Clement, 2001; Cross *et al.*, 2002; Leinwand, 2003; Mendelsohn and Karas, 2005; Pretorius *et al.*, 2005; Franconi *et al.*, 2007; 2011a,b; Regitz-Zagrosek and Seeland, 2012). It has also been shown that many genetic polymorphisms present sex–gender specificity (Myburgh *et al.*, 2012). It is not possible to examine all drugs, and thus we have focused our attention on some CV agents, as CV disease represents the major cause of mortality in women and in men (Nichols *et al.*, 2012), and SGDs in the prevention, diagnosis and outcomes of this disease have been demonstrated (Stramba-Badiale *et al.*, 2006).

Inhibitors of angiotensin converting enzyme (ACEIs), antagonists of angiotensin receptors 1 (ARBs), renin inhibitors and aldosterone antagonists

Sex–gender has an important influence on BP; premenopausal women have, for example, a lower arterial BP than age-matched men (Dubey *et al.*, 2002). However, a positive correlation between BP and coronary risk appears to be true for both men and women, regardless of age (Turnbull *et al.*, 2010). The prevalence and also the control of hypertension differ between the sexes. The assessment and management of cardiovascular (CV) risk can vary with patient sex, women being disproportionately affected (Turnbull *et al.*, 2011). It is not yet clear whether BP-lowering treatments provide similar protection against major CV events in men and women.

Table 1

Some sex–gender differences in the expression and/or activity of enzymes and transporters involved in drug metabolism or drug activity

Enzymes	Predominant sex	Substrates	Observations	References
Acetylcholinesterase	+ M (human) = rat	Acetylcholine		(Alves-Amaral *et al.*, 2010; Zimmer *et al.*, 2012)
Butyrylcholinesterase	+ F (rat) + M (human)	Succinylcholine, ester-type local anesthetics, cocaine		(Alves-Amaral *et al.*, 2010; Zimmer *et al.*, 2012)
Alcohol dehydrogenase 1	+ F	Cyclophosphamide		(Huang *et al.*, 2011)
Carboxylestererase 1	= (murine)	Methylphenidate, oseltamivir, irinotecan	Inducer: Phenobarbital	(Zhu *et al.*, 2009)
Carboxylesterase 2	= murine	Prasugrel, fans		(Zhu *et al.*, 2009)
Carboxylesterase 3	+ M (rat)	Irinotecan, capecitabine		(Huang *et al.*, 2011)
Carboxylesterase 4	+ M (rat)			(Huang *et al.*, 2011)
Catechol-O-methyl transferase	+ M	Dopamine, noradrenaline, adrenaline, levodopa, azathioprine		(Franconi *et al.*, 2007; Soldin and Mattison, 2009)
CYP1A2	+ M	Caffeine, clozapine, steroids, flutamide, lidocaine, mexiletine	Inducer: coffee, smoking, charcoal-grilled meat, omeprazole, carbamazepine, rifampicin Inhibitor: fluvoxamine cimetidine, ciprofloxacin, disulfiram, OC	(Anderson and Walton, 2005; Zanger and Schwab, 2013)
CYP2A6	+ F	Nicotine	In fertile age, is increased by OC	(Benowitz *et al.*, 2006)
CYP2B6	+ M	Cyclophosphamide, thiotepa, procarbazine,	Inducer: St. John's wort, rifampicin, phenytoin, phenobarbital	(Zanger and Schwab, 2013)
CYP2C9	=	Losartan, irbesartan, candesartan, valsartan		(Hallberg *et al.*, 2002; Anderson and Walton, 2005; Zanger and Schwab, 2013)
CYP2C19	=		OC influence it	(Anderson and Walton, 2005; Zanger and Schwab, 2013)
CYP2D6	+ M	Dacarbazine, cisplatin etoposide, etoposide, propranolol, metaprolol, tamoxifen, ondasentron, nortryptiline	Inhibitor: fluoxetine, paroxetine, quinidine	(Schwartz, 2007; Zanger and Schwab, 2013)
CYP2E1	+ M	Dacarbazine, cisplatin, etoposide		(Huang *et al.*, 2011)
CYP3A4 (liver)	+ F	Verapamil, midazolam, triazolam, alprazolam, nifedipine, zolpidem, imatinib, sunitinib, budesonide	Inhibitor: erythromycin, ethinylestradiol, ketoconazole Inducer: rifampicin, Ginkgo biloba, glucosteroids, statins, barbiturates, St. John's wort	(Huang *et al.*, 2011; Zanger and Schwab, 2013)
Dihydropyrimidine dehydrogenase	+ M	6-Mercaptopurine, fluorouracil		(Yamashita *et al.*, 2002; Franconi *et al.*, 2007)
Glutathione S-Transferase	+ M (rat)		Inducer: phenobarbital	(Higgins and Hayes, 2011; Huang *et al.*, 2011)

Table 1

Continued

Enzymes	Predominant sex	Substrates	Observations	References
Hydroxysteroid sulfotransferase	+ F (murine)		Inducer: caffeine only in intestine and liver of female rats	(Wu *et al.*, 2001; Maiti and Chen, 2003; Zhou *et al.*, 2012)
Aryl sulfotransferases	+ M (rat)	Oestrogen, thyroid hormones	Inducer: tamoxifen	(Maiti and Chen, 2003; Zhou *et al.*, 2012)
Thiopurine methyl transferase	+ M	6-Mercaptopurine		(Franconi *et al.*, 2007)
UDP-glucuronosyl-transferases	+ M (Ugt2b1 (liver) Ugt2b5/37/38 (kidney), and Ugt1a6 (lung) UGT2B17 + F Ugt1a1, Ugt1a5 (liver) Ugt1a2 (kidney) brain Ugt2b35	Steroid hormones, acetaminophen	Influenced by diet Inducer: smoking and alcohol	(Buckley and Klaassen, 2007; Gallagher *et al.*, 2010; Navarro *et al.*, 2011)
Renal Transporters				
Organic Anion Transporter 1	+ M rat = in rabbit	ACEI, ARB, thiazides, furosemide, penicillins, cephalosporins, quino-lones, tetracyclines, aminoglycosides, macrolides, cimetidine, ranitidine, fluvastatin, pravastatin, simvastatin	Inhibitor: rifampicin	(Buist *et al.*, 2002; Emami Riedmaier *et al.*, 2012)
Organic Anion Transporter 2	+ F rat = rabbit	Loop and thiazide diuretics, cephalosporins, tetracyclines, erythromycin, 5-fluorouracil		(Groves *et al.*, 2006; Emami Riedmaier *et al.*, 2012)
Organic Anion Transporter 3	= rat, rabbit	Bumetanide, ethacrynate, furosemide, penicillin, diclofenac, ibuprofen, indomethacin, ketoprofen		(Emami Riedmaier *et al.*, 2012)
Organic Anion Transporter 5	+ F (rat)	Furosemide, benzylpenicillin, diclofenac, ibuprofen, salicylate		(Emami Riedmaier *et al.*, 2012)
Urate Transporter 1	+ M (rat, human)	Salicylate, phenylbutazone, sulfinpyrazone, indomethacin, losartan, pratosartan, telmisartan, furosemide, benzylpenicillin		(Emami Riedmaier *et al.*, 2012)
Liver and intestinal transporters				
Oatp1	= rat			(Rost *et al.*, 2005)
Oatp2	= rat			(Rost *et al.*, 2005)
Oatp4	+ F = (rat)			(Li *et al.*, 2002; Rost *et al.*, 2005)
Multidrug resistance protein				
Mrp2	+ F		High-fat diet reduces hepatic Mrp2 expression only in female	(Rost *et al.*, 2005; Lu and Klaassen, 2008; Kong *et al.*, 2012)
Mrp3	+ F			(Rost *et al.*, 2005)

F = female, M = male.

Differences in CV risks between sexes are unlikely to reflect differences in response to BP-lowering treatments (Turnbull *et al.*, 2008).

ACEIs and ARBs are integral components of CV therapy. The renin angiotensin system (RAS) shows sexual dimorphism; sex hormones affect the RAS at multiple levels. In particular, oestrogens increase the availability of angiotensinogen and plasma levels of angiotensin II, but decrease renin and ACE activities, and the expression of angiotensin receptor 1, while androgens up-regulate the RAS system (Fischer *et al.*, 2002). A lower percentage of women have been included in clinical trials with ACEIs and ARBs in comparison with men, and many of these were not designed to incorporate SGDs (Stramba-Badiale, 2009; Seeland and Regitz-Zagrosek, 2012). One meta-analysis showed that ACEIs are less effective in reducing mortality in women with symptomatic heart failure than in men, whereas these agents do not modify the survival rate in women with asymptomatic heart failure (Shekelle *et al.*, 2003). In women at high CV risk, ACEIs reduce CV events when used for secondary prevention (Seeland and Regitz-Zagrosek, 2012). However, results from an Australian study demonstrated that ACEIs decrease CV events in men but not in women (Wing *et al.*, 2003). More recently, it has also been shown that some sex disparities depend on genetic differences. A genetic variant of the ACE-1 enzyme (I and D alleles) affects the therapeutic response to ACEIs; ACEIs are more renoprotective in women with the D/D genotype compared to D/D men, while in D/D men, they are more effective in those with the I/D than the I/I genotype (Ruggenenti *et al.*, 2008). The ACE gene I/D polymorphism, which is linked to increased plasma levels of ACE and with a major risk for CV disease (Kumar *et al.*, 2009), also affects the hypotensive effect of hydrochlorothiazide in a sex–gender specific manner. The genotypes associated with the greatest responses to hydrochlorothiazide are II homozygotes and D/D in women and men, respectively (Schwartz *et al.*, 2002).

During treatment with ACEI, cough and angioedema are more frequent in women than in men (Slater *et al.*, 1988; Mackay *et al.*, 1999). Recently, it has been observed that the XPNPEP2 C-2399A genotype, which in individuals produces higher plasma levels of aminopeptidase-inactivated metabolites, is associated with an increased frequency of ACEI-associated angioedema in all men, especially black men, but not in white men and women (Woodard-Grice *et al.*, 2010). However, ACEI-related cough seems to be associated with polymorphism of the bradykinin B_2 receptor (for correct receptor nomenclature see Alexander *et al.*, 2013), the effect of this polymorphism being sex-specific (Mas *et al.*, 2011). Finally, the majority of women discontinue ACEI therapy due to cough, while the majority of men stop treatment because of hypotension (Shah *et al.*, 2000).

Another class of compounds that affects the RAS is defined by renin inhibition. The first direct inhibitor of renin, aliskiren, shows the same efficacy as an anti-hypertensive in men and women. Even though the area under the plasma concentration–time curve and maximal concentration of aliskiren were lower in men than in women, adjustment of individual values for overall mean body weight abolished these gender differences (Jarugula *et al.*, 2010; Seeland and Regitz-Zagrosek, 2012).

Aldosterone, the primary mineralocorticoid secreted by the adrenal gland, is also implicated in the pathogenesis of CV disease (Rocha and Stier, 2001). Results of the Framingham Heart Study indicated that serum levels of aldosterone are directly related to cardiac wall thickness in women, but not in men (Vasan *et al.*, 2004), suggesting that women are more at risk from the harmful effects of aldosterone than men (Duprez, 2004). In two clinical trials, RALES (Randomized Aldactone Evaluation Study) and EPHESUS (Eplerenone Post-Acute Myocardial Infarction Heart Failure Study), it was shown that spironolactone and eplerenone, selective aldosterone antagonists, were effective at reducing mortality in heart failure patients (Pitt *et al.*, 1999; 2003). However, it is not yet known whether these agents have sex-specific effects in relation to treatment of post-myocardial infarction. At 30 days, when all causes of mortality were considered, the eplerenone study showed a trend towards a greater benefit for women in comparison with men. However, at 16 months, when CV death or hospitalization for CV events was considered, there was a trend for a greater benefit in men than in women. The RALES trial, which examined the effect of spironolactone in symptomatic heart failure patients, showed no sex differences. However, it is important to note that only about 30% of the patients participating in these trials were women, therefore, no firm conclusions can be drawn from the results. In animal models, the aldosterone antagonists reduced the infarct size in male, but not female mice and rats (Rigsby *et al.*, 2007; Frieler *et al.*, 2012). Additionally, spironolactone was shown to lower BP only in male rats on a high-salt diet (Michaelis *et al.*, 2012), whereas eplerenone is more effective in reducing myocardial infarct-induced cardiac remodelling in female rats, and also, at restoring altered gene expression (Kanashiro-Takeuchi *et al.*, 2009).

Calcium channel blockers

Calcium channel blocking agents are mainly prescribed for CV disease, particularly for hypertension and as a prophylaxis against angina. Some of these agents, such as verapamil and amlodipine, show sexual dimorphism in their pharmacokinetics. In particular, men have a faster clearance of sustained release or p.o. administered verapamil than women (Krecic-Shepard *et al.*, 2000), but not after i.v. injection. Interestingly, the mean plasma level of each verapamil enantiomer is higher in women than in men at all time points after administration of a controlled release preparation (Gupta *et al.*, 1995). Hence, the different effects seen after p.o. and i.v. administration could be attributed to the higher activity of CYP3A4 or lower activity of P-glycoprotein in women compared with men, or both factors (Dadashzadeh *et al.*, 2006). Indeed, it has been shown that the bioavailability of amlodipine is slightly higher in women than in men, but these differences were attributed to the lower body weight of women, because when data were adjusted for weight, the bioavailability did not differ (Abad-Santos *et al.*, 2005). There are a few sex–gender pharmacodynamic differences: women treated with verapamil, especially the elderly, experienced a greater BP reduction than men (Jochmann *et al.*, 2005). Indeed, Krecic-Shepard *et al.* (2000) showed that in hypertensive women, verapamil produces a greater heart rate than in men. The long-acting calcium antagonist amlodipine, after

adjustment of dose for body weight, leads to a larger BP reduction in women than in men, and this depends on the use of hormonal replacement therapy (Kloner *et al.*, 1996). The same study showed that women have a higher incidence of oedema than men. Finally, in the HOT (Hypertension Optimal Treatment) study with felodipine, which was administered alone or, if necessary, in combination with other antihypertensives, the target diastolic BP was not reached, with or without the addition of aspirin. It was also demonstrated that the incidence of acute myocardial infarction is significantly less in women with a lower diastolic BP target (<80 and <85 mmHg) compared with those with a higher BP target value (<90 mmHg). This trend was not significant in men, although the effect of aspirin was more marked (Kjeldsen *et al.*, 2000). Finally, a recent study showed that the combination olmesartan and amlodipine induces a small but significant reduction in diastolic and systolic BP, the reduction being higher in women than in men (Schmieder and Bohm, 2011). With another dihydropyridine calcium antagonist, nifedipine, more drug-related adverse events were observed in women (15.8%) than in men (9.8%) (Fan *et al.*, 2008). In contrast, pharmacokinetic parameters determined after a single dose of diltiazem did not differ between men and women (Yeung *et al.*, 1993; Saenz-Campos *et al.*, 1995), although some differences in haemodynamic responses have been detected (Klassen *et al.*, 1995). However, these studies were very small, and so it is difficult to reach any definitive conclusion.

β-Adrenoceptor antagonists

The activity of the CV system is also strictly controlled by the noradrenergic system, which presents numerous SGDs. Generally, sympathetic nerve activity is more elevated in men than in women of the same age (Hart and Joyner, 2010). In young men, but not in young women, muscle sympathetic nerve activity is positively related to total peripheral resistance (Hart and Joyner, 2010). Women have an elevated cardiac noradrenaline spillover, indicating that they have a greater cardiac-specific sympathetic activation than men (Mitoff *et al.*, 2011). Women are less responsive to sympathetic vasoconstrictor activity than men (Momen *et al.*, 2010). Importantly, β_2-adrenoreceptor sensitivity is increased in young women compared with men (Kneale *et al.*, 2000), and young women have a higher density of β_2-adrenoreceptors in lymphocytes (Wheeldon *et al.*, 1994; Mills *et al.*, 1996). These differences in β_2-adrenoceptor signalling could explain the greater vasoconstrictor sensitivity to noradrenaline in men.

β-Adrenoceptor antagonists are among the most widely prescribed drugs. In particular, they show numerous sex–gender pharmacokinetic differences, which predominate in those agents metabolized by CYP2D6, such as metoprolol and propanolol (Luzier *et al.*, 1999). Notably, oral contraceptives (OC) increase the plasma concentration of metoprolol (Franconi *et al.*, 2011a). β-Adrenoceptor antagonists elevate aortic wave reflection both in young men and women, but they are more effective in women (Lieber *et al.*, 2010; Casey *et al.*, 2011; 2012); it is notable that the effects of these antagonists are mediated by sex specific mechanisms (Casey *et al.*, 2012). However, these clinical studies with β-adrenoceptor antagonists have involved only a small number of women and often their number is not sufficient to reach significance. This could also explain the equivocal results obtained on the efficacy of β-adrenoceptor antagonists in treatment of heart failure (Seeland and Regitz-Zagrosek, 2012).

Endothelin-1 antagonists

The potent vasocostrictor endothelin-1 (ET-1) presents some sex–gender specificity, as recently reviewed (Seeland and Regitz-Zagrosek, 2012). In particular, in animal models, males express more ET-1 and have a greater endothelin receptor A-mediated response (Kittikulsuth *et al.*, 2013). Men have higher concentrations of circulating ET-1 and a more pronounced ET-mediated coronary vasoconstriction than women. In addition, genetic polymorphisms of the ET system are more likely to be associated with hypertension and renal injury in women than in men (Kittikulsuth *et al.*, 2013). Some SGDs have also been seen during the treatment of pulmonary hypertension with endothelin antagonists, indicating the superior therapeutic benefit of these drugs in women compared to men (Gabler *et al.*, 2012).

Statins

Statins are global leaders as therapeutics for dyslipidemia, being largely used for the primary and secondary prevention of CV disease. They inhibit the rate-limiting enzyme hydroxymethylglutaryl coenzyme A (HMG-CoA) reductase. Notably, in experimental models, oestrogens prevent the conversion of HMG-CoA to mevalonate (Ness and Chambers, 2000). However, the use of statins for primary prevention of CV disease among women is still a matter of debate (Mosca, 2012), because only a few women have ever participated in primary prevention trials, and women have a lower short-term absolute risk of CV events, strengthening the challenge of women being under-represented in clinical trials. Indeed, a recent meta-analysis suggests that statins could have some benefit in the primary prevention of CV disease in women (Kostis *et al.*, 2012). For primary prevention, it was found that the average number of patients who need to be treated to observe one bad outcome over 4 years was 148 women compared to 43 men, while for secondary prevention, these numbers are 36 for women and 29 for men (Kostis, 2012). However, the Kostis' meta-analysis covered a relatively short study period, which means there are still some concerns over the long-term safety of statins. In fact, a longer term study of statin use for primary prevention showed a potential risk of diabetes mellitus (Sattar *et al.*, 2010) depending on the dose and on the individual statin administered (Navarese *et al.*, 2013). Whereas in another meta-analysis, the benefits of statin treatment and risk of diabetes were less clear in women than in men, especially if the statins were used for primary prevention and in young women (Ma *et al.*, 2012). Muscular side effects, such as myalgia, with or without an elevation in serum CK, cramps and weakness, have frequently been associated with the use of statins, with myopathy being more frequent in women than in men (Bellosta *et al.*, 2004; Baigent *et al.*, 2010). These side effects have led to approximately 30% of the symptomatic patients ceasing to take the statins, with the dropout rate being higher in women than in men (Rosenbaum *et al.*, 2012).

Aspirin and antiplatelet therapy

Numerous SGDs have been described for the biology of platelets (Johnson *et al.*, 1975; Faraday *et al.*, 1997; Kurrelmeyer *et al.*, 2003; Yee *et al.*, 2005; Eidelman *et al.*, 2010). In particular, it has been observed that after puberty, women have consistently more platelets than men, and the age-induced decrease in platelet count is more in men than in women (Biino *et al.*, 2013). Both megakaryocytes and circulating platelets express receptors for sex steroids (Miller *et al.*, 2008), but their role in platelet biology has not been clarified. Indeed, the menstrual cycle does not affect platelet aggregation (Kurrelmeyer *et al.*, 2003; Eidelman *et al.*, 2010), while OC promote it (Braunstein *et al.*, 2002). Experimental data in mice have shown that oestrogens through oestrogen receptor (ER)-α decrease platelet aggregability *ex vivo* and *in vivo* (Valera *et al.*, 2012). In addition, oestrogens modulate the expression of platelet proteins, including β1 tubulin, which may affect platelet production and activation (Valera *et al.*, 2012). Tamoxifen inhibits platelet aggregation (Nayak *et al.*, 2011), suggesting that oestrogens could play a role in platelet biology. Howevwe, the findings of Valera *et al.* (2012) and Nayak *et al.* (2011) seem to be contradictory; it is known that tamoxifen behaves as a mixed agonist/antagonist of oestrogen receptors depending on the sensitivity of the tissue to oestrogen (Powles *et al.*, 1996; Cohen *et al.*, 2008).

Genetic polymorphisms for platelet glycoproteins are associated with risk of atherothrombotic events (Weiss *et al.*, 1996; Bray, 2000; Zotz *et al.*, 2000), but it is not known if they are influenced by sex–gender. However, women heterozygotes and homozygotes for the GPIb-α-5C allele, have a higher incidence of a composite end point (death, myocardial infarct or unstable angina) compared with those homozygous for the GPIb-α-5T allele (Bray *et al.*, 2007). Hormone replacement therapy is associated with a 46% lower adjusted CV risk in women with the -5C allele versus the -5TT genotype (Bray *et al.*, 2007).

The SGDs in aspirin and antiplatelet therapy have recently been reviewed (Franconi *et al.*, 2011b; Wang *et al.*, 2012) and it has emerged that there is a gap in the systematic knowledge regarding platelet biology, genomics and response to antiplatelet therapy, which is partly due to an underrepresentation of women in clinical trials (Melloni *et al.*, 2010). This deficiency should be overcome by increasing our knowledge of platelet biology, including the role of platelet oestrogen and androgen receptors and the influence of pharmacogenomics.

Adverse drug effects (ADEs)

Women have a higher rate and a major severity of ADEs (Pirmohamed *et al.*, 2004; Patel *et al.*, 2007; Franconi *et al.*, 2011b). Indeed, risk factors for ADE, such as polytherapy, aging and depression, are more frequent in women than in men (Pirmohamed *et al.*, 2004; Patel *et al.*, 2007; Zender and Olshansky, 2009; Sikdar *et al.*, 2010; Franconi *et al.*, 2011b). Female sex–gender appears to be a potential risk factor for ADEs, such as iatrogenic long QT syndrome, thiazolidinedione-induced bone fracture and iatrogenic systemic lupus erythematosus (Borchers *et al.*, 2007; Jones *et al.*, 2009; Rivero and Curtis, 2010; Franconi *et al.*, 2011b). Numerous medications can prolong the QT interval, such as antiarrhythimcs, anti-infective drugs, antipsychotics, gastrokinetic stimulants, antihistaminics and opioid analgesics. Notably, the SGDs in QT duration are age- and hormone-dependent (Kurokawa and Furukawa, 2013). Susceptibility to drug-induced arrhythmias is higher when the oestrogen level is higher (James *et al.*, 2007) and lower when the progesterone level is high (Janse de Jonge *et al.*, 2001; Nakagawa *et al.*, 2006). Some SGDs may arise directly from cardiac tissue; for example female hearts express fewer of the K ion channel subunits hERG, minK, $K_{IR}2.3$, $K_V1.4$, K_V channel-interacting protein 2 (KChIP2), SUR2 and $K_{IR}6.2$, and also connexin43 and phospholamban compared with male hearts (Di Diego *et al.*, 2002; Fish and Antzelevitch, 2003; Gaborit *et al.*, 2010; Nattel *et al.*, 2010). Additionally, hypokalaemia, hyponatraemia induced by antihypertensive agents, nausea, vomiting and haematological toxicity induced by antiblastics, bleeding induced by anticoagulants and salycilates, antipsychotic drug-induced weight gain, and metabolic syndrome are more frequent and severe in women than in men (van Kuilenburg *et al.*, 2004; Haack *et al.*, 2009; Regitz-Zagrosek and Seeland, 2012). In conclusion, ADEs represent a source of greater health concern in women than in men and, therefore, need to be investigated further and in more depth.

Perspectives

The epidemiology, natural history, prophylaxis and therapy of diseases are strongly influenced by sex–gender, and therefore, it is time to include sex–gender at each stage of drug development. In women, sex steroid hormone fluctuations should be included in the design of studies, but it should also be mandatory to determine whether females are using exogenous hormones (including phytoestrogens) and drugs that interfere with hormonal signalling in view of the bidirectional relationship between sex hormones and drugs. Of course, men should be included in clinical trials for the diseases where the disadvantage predominates in the male sex, as in the case of breast cancer and hemicranias.

In the future, it is of major importance to carry out definitive studies in order to gain a more detailed knowledge of SGDs. The design of clinical and preclinical studies should have a gender-based approach with a view to reaching proper conclusions for both sexes and to reduce the time for translation of research results into daily clinical practice. Furthermore, it is vitally important to reduce ADEs because of their high individual, social and economic effects. Psychological factors and the environment appear to be involved in the pathogenesis and progression of CV diseases, so the influence of specific elements should be evaluated with the aim of tailoring therapies to an individual's needs and concerns. At a fundamental level, it is a matter of paramount importance to increase drug efficacy, safety profile, adherence and compliance to therapy.

Acknowledgements

Supported by a grant of Legge Regionale n. 7: 'Promozione della ricerca scientifica e dell'innovazione tecnologica in

Sardegna' and by a grant of Regione Sardegna 'Progetti difarmacovigilanza attiva, finanziabili attraverso i fondi fv 2008/09'. We are grateful to the Major of Osilo and all Municipal Hall for the laboratory space that they dedicate to the National Sex –Gender Laboratory.

Conflict of interest

None.

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